Sex-Related Differences in Lower Extremity Peripheral Artery Disease

A review of differences in clinical presentation and outcomes after surgical revascularization and endovascular procedures in women as compared with men.

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Lower extremity peripheral artery disease (PAD) is a growing epidemic, affecting approximately 8 to 12 million individuals in the United States and more than 200 million people worldwide.[1,2] The prevalence of PAD in women has traditionally been considered to be less than or equal to that of men. However, recent studies demonstrate an expected rise in the total population burden of PAD in women.[3] Yet, PAD remains underdiagnosed in women, and women have been underrepresented in several PAD revascularization trials.

The traditional risk factors for development of PAD include diabetes mellitus, cigarette smoking, advanced age, dyslipidemia, and hypertension.[4] Although these conventional risk factors result in PAD development in women similarly as they do in men, a growing body of evidence has demonstrated additional comorbidities that are prevalent in women with PAD, such as depression and inflammation.[5] Such risk factors are not routinely evaluated in PAD studies, and future trials are necessary to determine whether an association exists between these "novel" risk factors and the development of PAD in women.

Intermittent claudication is considered the hallmark symptom of PAD, but women may often be asymptomatic or present with atypical symptoms (eg, leg muscle symptoms at rest and with exercise).[3] Also, women with PAD are more likely to be older at presentation compared to their male counterparts, present with critical limb ischemia (CLI), are less likely to undergo surgery, and are more likely to undergo amputations.[6]

OUTCOMES AFTER SURGICAL REVASCULARIZATION

After lower extremity bypass surgery, women have a higher rate of graft failure, wound complications, and limb loss when compared to men.[7] Additionally, elevated baseline levels of C-reactive protein and fibrinogen have been shown to be associated with inferior vein graft patency in women. This suggests a potential interaction between sex and inflammation in the healing response of vein grafts after lower extremity bypass surgery.[8] In clinical practice, women with elevated preoperative C-reactive protein and fibrinogen levels may benefit from more aggressive postoperative graft surveillance protocols.

ENDOVASCULAR OUTCOMES

Recent studies evaluating sex differences in endovascular treatment outcomes have demonstrated that women are older and more likely to present with CLI compared to men, who most commonly presented with claudication.[9] In addition, women were more likely to have multilevel disease and required more femoropopliteal interventions. There does not seem to be a mortality difference between men and women after endovascular treatment for PAD. Some studies suggest increased periprocedural adverse events, including vascular complications (dissections), bleeding, transfusions, and embolism in women.[9,10] However, a recent propensity score–matched analysis demonstrated higher complications in male patients, with only an increased rate of blood transfusions in women.[11] This finding is particularly important because it demonstrates that although women may present with more advanced PAD, the outcomes may not

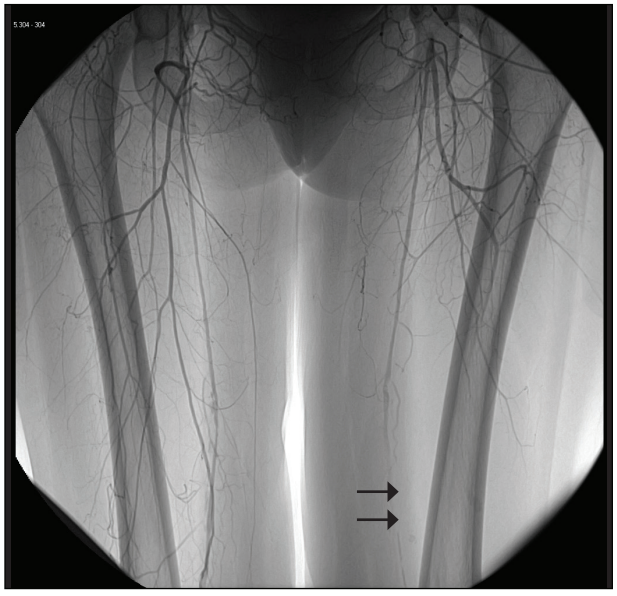

Figure 1. Angiogram showing near occlusion of the distal left SFA.

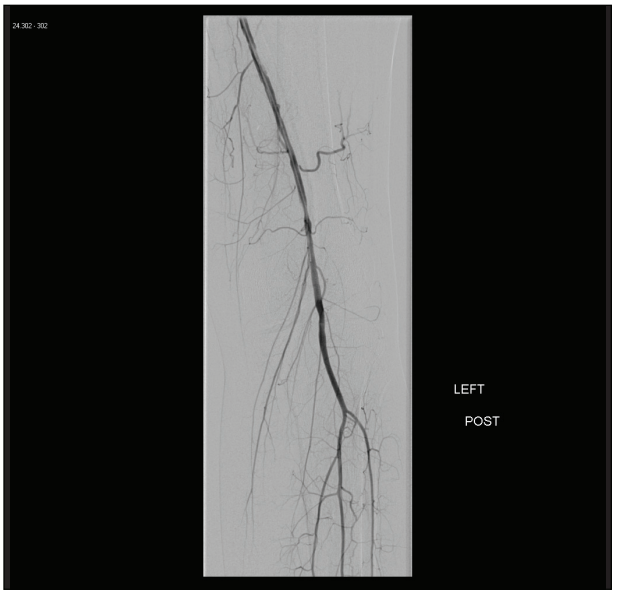

Figure 2. Angiogram showing a non–flow-limiting dissection after PTA using a low compliance balloon.

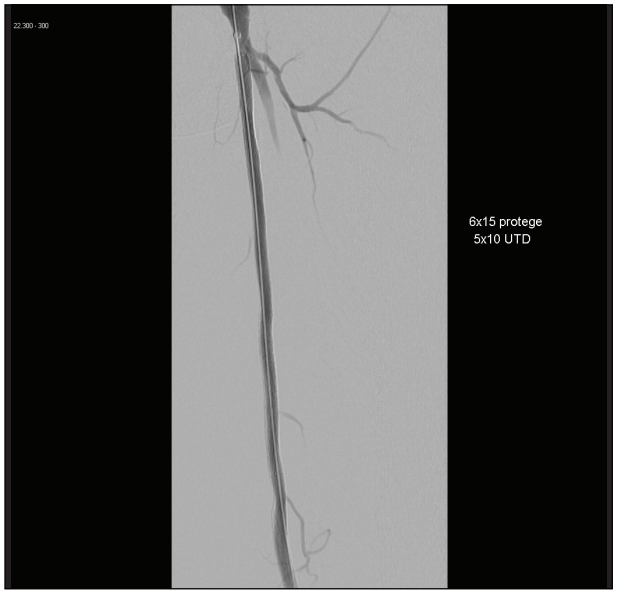

Figure 3. Eighteen months later, two 6- X 150-mm nitinol stents were placed in the left SFA.

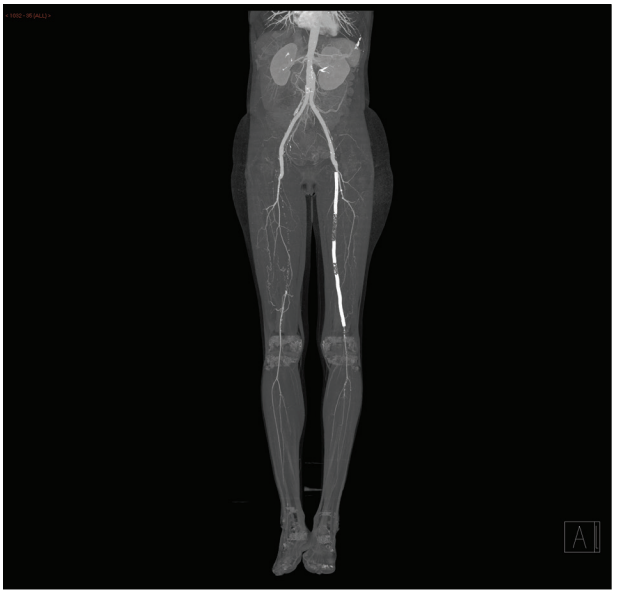

Figure 4. CTA 2 years later, after placement of a 5- X 50-mm self-expanding covered stent in the proximal popliteal artery.

differ when compared to their male counterparts, who tend to be younger and have a less advanced PAD. This only increases the need for earlier diagnosis and intervention for women who have PAD. In a different propensity score–matched analysis, women were 1.5 times more likely to require reintervention when compared with men.[12] Although the exact reason for this is not known, it may be due to the difference in vessel size. In fact, it has been shown that the caliber of all vessels in the lower extremity of women are statistically significantly smaller than those in men.[13] These findings argue for potentially more aggressive clinical follow-up with female patients after endovascular therapy for PAD.

OUTCOMES AFTER DCB ANGIOPLASTY

Prospective randomized controlled trials have demonstrated superior outcomes for the treatment of femoropopliteal lesions with drug-coated balloon (DCB) angioplasty versus percutaneous transluminal angioplasty (PTA).[14,15] However, the US Food and Drug

Administration summary of safety and effectiveness data from the LEVANT 2 trial demonstrated a reduced treatment effect in women as compared with men.[16] Interestingly, in the German subgroup analysis of the LEVANT 2 trial, women benefited more from treatment with DCB angioplasty compared to men.[17] Other studies also demonstrate conflicting results and show female sex as a prognostic indicator for restenosis after DCB angioplasty.[18,19] Further investigation is necessary in order to detect a potential sex-related difference with respect to outcomes following DCB angioplasty.

CASE EXAMPLE

A 47-year-old woman presented with left lower extremity claudication. On angiography, she was found to have near occlusion of the distal left superficial femoral artery (SFA) (Figure 1). The SFA occlusion was crossed in the subintimal plane using a 5-F catheter and 0.035-inch angled hydrophilic guidewire. After PTA to 4 mm, using a low compliance balloon, there was a non–flow-limiting dissection (Figure 2).

The patient returned 18 months later with recurrent symptoms. Two 6-mm nitinol self-expanding bare-metal stents (Protege, Medtronic) were placed from the femoral bifurcation to the adductor canal (Figure 3). Three years later, she required two reinterventions, including laser atherectomy and placement of a self-expanding covered stent (Viabahn, Gore & Associates) in the proximal popliteal artery (Figure 4).

This case demonstrates the small size of the arteries in women and the tendency to experience complications such as dissection. The case also exemplifies the need for additional endovascular procedures, as women typically require more interventions as compared with men.

CONCLUSION

Sex-related differences are present in the development, presentation, and outcomes of PAD. Women with PAD are more likely to present with more advanced disease and are older at the time of diagnosis. This is due to the absence of routine PAD screening in women and potentially different risk factors and presenting symptoms.

Outcomes after endovascular treatment in women are promising. More research is necessary to determine whether women and men have similar outcomes after DCB angioplasty and to identify the potential subgroup of women who may require more aggressive follow-up and reintervention. Awareness of these differences can help identify more women who may be at risk for PAD, with intervention performed earlier. Further clinical trials are needed to identify the key sex-related differences that may explain the difference in outcomes between men and women with PAD. ■

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Disclosures: Consultant to Proteon Therapeutics, Terumo Interventional Systems, Daiichi Sankyo; speaker for Cook Medical, Medtronic, and Gore & Associates; unrestricted grants from Siemens Healthcare.